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The Physician's Role in Treating Epidermolysis Bullosa (EB):

Although a rare disorder, you may see rare *Epidermolysis Bullosa* during your career. Here are a few crucial things for you to know. These will ensure the health and well being of your patients with EB. Many routine techniques utilized in your day-to-day care of patients will need to be adapted to the special needs of the EB population. The following guidelines are provided to you as a resource and will give you basic information when treating an EB patient.

What is Epidermolysis Bullosa (EB)?

Epidermolysis bullosa (EB) is a genetic skin disorder characterized by blister formation from mechanical trauma. There are 4 main types: EB Simplex, Junctional EB, Dystrophic EB, and Kindler Syndrome, with additional sub-types identified. Some type of EB occurs in an estimated 1 out of every 50,000 live births. The disorder occurs in every racial and ethnic group throughout the world and affects both sexes equally. There is a spectrum of severity, and within each type, one may be either mildly or severely affected. EB ranges from being a minor inconvenience requiring modification of some activities to being completely disabling and, in some cases, fatal.

Friction causes blister formation. Simply swallowing food or wearing clothing with seams can result in agonizing wounds. They can form anywhere on the surface of the skin, within the oral cavity and in more severe forms may also involve the external surface of the eye, as well as the respiratory, gastrointestinal and genitourinary tracts. In some forms of the disease, disfiguring scars and disabling musculoskeletal deformities occur.

Currently, ***there is no cure for EB***. Supportive care includes daily wound care, bandaging, and pain management as needed.

What Are the Types of EB?

EB Simplex (EBS)

EB Simplex is usually dominantly inherited, and involves disorders of the genes for Keratins 5 and 14 and plectin. Blistering occurs within the uppermost layer of the skin within the epidermis (intraepidermal). EBS may be localized to the hands and feet or there may be a generalized distribution, with relatively mild internal involvement. Those with EBS may have thickened calluses on the palms and soles, oral blistering during infancy and rough, thickened fingernails/toenails.

Junctional EB (JEB)

Junctional EB is recessively inherited, and involves disorders of the several components of the junction between the epidermis and dermis such as Laminin 5 (now 332), plectin, and $\alpha 6\beta 4$ integrin. Blisters occur between the upper and lower layer of the skin (at the level of the lamina lucida within the basement membrane zone) and skin involvement is generalized in Junctional EB. There are three subtypes of JEB: Herlitz, non-Herlitz and JEB with Pyloric Atresia.

Junctional Herlitz EB is a very severe form of EB. Death often occurs during infancy due to overwhelming

infection (sepsis), malnutrition, dehydration, electrolyte imbalance or complications resulting from internal blistering. There is a wide spectrum of non-Herlitz JEB. Infants presenting with pyloric atresia will have trouble with feeding and abdominal distension as neonates and are surgical emergencies.

Dystrophic EB (DEB)

Dystrophic EB can be either dominantly or recessively inherited, and involve defects in Type VII collagen. Blisters occur within the lower layer of the skin (sub-lamina densa Basement membrane Zone separation).

Dominant Dystrophic EB (DDEB): Blistering may be localized to the hands, feet, elbows and knees or it may be generalized. Common findings include scarring, milia (*tiny white bumps*), mucous membrane involvement, and abnormal or absent nails.

Recessive Dystrophic EB (RDEB): Typically more generalized and severe than DDEB. In addition to the findings of DDEB, common manifestations include malnutrition, anemia, esophageal strictures, growth retardation, webbing or fusion of the fingers and toes causing mitten deformity (pseudosyndactyly) and loss of function, development of contractures, malformation of teeth, microstomia and eye involvement. The risk of squamous cell carcinoma is greatly increased in this group.

Kindler Syndrome

Kindler Syndrome is recessively inherited, and involves disorders of the genes for Kindlin-1. The blistering can occur at any layer of the skin. Kindler Syndrome involves a generalized distribution, with internal involvement that can include colitis. Those with Kindler syndrome may have thickened calluses on the palms and soles and mottled pigmentation of neck and chest.

How is EB diagnosed?

Avoid making specific diagnosis of the type of EB based on presentation in the neonatal period, as all three types of EB may look alike in this age group. When EB is suspected, a skin biopsy should be obtained by a dermatologist to confirm the diagnosis. This procedure includes numbing an area, inducing a fresh blister if necessary, taking a small sample of skin for direct Immunofluorescence and electron microscopy by a knowledgeable pathologist. Currently, Beutner Labs, Inc. and Stanford University are performing diagnostic EB testing.

Prior to obtaining the sample, the lab should be contacted, to provide detailed instruction on sample collection.

To identify exactly where the split (cleavage plane) is in the skin and which proteins are involved (absent or diminished), **Immunofluorescence** (IF) antigenic mapping and monoclonal antibody studies are performed. Monoclonal antibodies are used to bind to certain antigens (proteins) that are normally present in the skin. If specific antigens or proteins are missing, there will be an absence of staining, identifying the missing protein and supporting the diagnosis of the type of EB.

Transmission Electron Microscopy involves the use of a high powered microscope to study the sample of skin to identify specific structural defects. This is still considered the "gold standard" for diagnosis.

Upon identification of type, **DNA analysis** may be done to identify the specific genetic mutation and to determine the mode of inheritance. This is helpful information in regard to future family planning. Once the genetic mutation is identified in a family, prenatal diagnosis of subsequent pregnancies is possible via Preimplantation genetic diagnosis (PGD), chorionic villus sampling, or amniocentesis.

The sample can be matched against the previously identified mutation by a genetic molecular lab. GeneDx is performing this testing commercially at this time in the USA.

Unfortunately, these tests are very expensive and results take several weeks.

It is helpful to locate sources of support for the family, such as extended family, other parents with children affected by EB and organizations such as DebRA of America (www.debra.org). These can help alleviate stress by providing education and resources to affected individuals and their caregivers.

How is EB managed?

Because EB can involve many systems of the body, parents and health professionals must take an interdisciplinary team approach to the treatment of an EB patient which could include the primary care physician, dermatologist, nurse, pediatric dentist, gastroenterologist, dietitian or nutritionist, plastic surgeon, psychologist or social worker, genetic counselor and others. Intense and total patient care often must be provided, particularly for young children. The severe forms of EB require meticulous nursing care which is similar to that given to burn patients. The parents often provide much of this care; however, the education of all people who have contact with the patient including teachers, relatives, baby sitters, is essential.

Treatment of EB is directed towards the symptoms and is largely supportive. This care should focus on prevention of infection, protection of the skin against trauma, attention to nutritional deficiencies and dietary complications, minimization of deformities and contractures, and the need for psychological support for the entire family. Many persons with milder forms have minimal symptoms and may require little or no treatment.

Issues to Consider:

By definition, inherited EB is a genetically transmitted disorder characterized by marked fragility of the skin. Any trauma, no matter how minimal it may seem, is likely to cause the skin of an EB child or adult to tear or blister. The following are recommended ways to avoid or minimize this problem:

Reducing Friction - Extreme care should be employed in handling the skin of any patient with EB. This includes lateral traction or anything else that leads to increased friction or surface injury to the skin. Infants are particularly prone to this; excessive manipulations should be avoided, as well as any firm handling of the skin. Additionally, infants should not be completely undressed for exam, as they may cause themselves injury by rubbing skin to skin as they kick and move

Blood Draws and Injections – Avoid even modest rubbing of the skin, as in cleansing prior to blood-drawing or injections. When alcohol or another cleansing agent is required, it should be gently dabbed onto the affected areas, rather than rubbed or wiped. The tourniquet should be placed over loosely applied roller gauze, to protect the underlying skin. Children with EB should be given all routine vaccinations. With respect to IM injections, gentle pressure may be applied in place of vigorous massage of the injection site.

Blood Pressure – Do not use a blood pressure cuff directly on the skin. Place it over roller gauze that is loosely applied to the patient's arm, in a wider band than the width of the cuff to be used. This will help prevent the edges of the cuff from causing injury

Non-Adhesive Bandages and Dressings – Do not apply any adhesive or semi-adhesive dressings, bandages, Band-aids, or tape directly to the surface of the skin. Instead, wounds should be covered with an appropriate non-adhesive dressing (to include Vaseline impregnated gauze or any of several synthetic non-adherent dressing such as Telfa® or Mepilex®) and then further wrapped loosely with roller gauze. This can be secured by using a tubular dressing retainer. Tape can only be used gauze to gauze- it cannot be applied directly to the skin.

Additionally, adhesive-backed monitors leads are problematic. The adhesive portion must be placed on hydrogel (Vigilon®) or completely removed, and the leads can be held in place with Mepilex Transfer®, Mepilex Light® or Mepitac®, adhesive-free silicone products.

Areas chronically prone to mechanical injury, such as the elbows and knees, are best kept protected with loosely applied tubular gauze to cushion the skin. Foam or gel dressings may be incorporated into the bandages over the knees and elbows to add padding. This is particularly important in patients with the more severe, generalized forms of inherited EB, and babies that are starting to crawl and walk.

Keeping the Skin Cool - Nothing hot should ever be applied to the skin of a patient with EB, since this may result in immediate blister formation. In particular, bath water should be no warmer than body temperature. Great care should be taken in the bathing of infants with this disease, since their skin is especially sensitive to such mechanical and thermal insult.

Most patients with inherited EB, even those with the most localized forms of this disease, develop increased numbers of blisters during periods of warmer weather. Patients should avoid prolonged exposure to ambient heat and humidity. If possible, air conditioned environments should be sought whenever possible.

Preventing Infection -Inherited EB is not an infectious disease, so it cannot be transmitted to anyone participating in an EB patient's care. However, open sores on the skin, regardless of the cause, often become secondarily infected with bacteria, most commonly *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This is certainly the case with EB and may intermittently result in otherwise unexplained worsening of the disease.

Signs of secondary infection of the skin include:

1. The presence of redness (so-called "cellulitis") surrounding a blister or open sore, or a red streak ("lymphangitis") spreading linearly from an EB lesion towards a more central part of the body.
2. Unexplained fever or chills.
3. Yellowish or honey-colored crusting on one or more lesions.
4. Evidence of pus, either on the surface or as discharge from an EB lesion.
5. Foul smelling odor.

The presence of secondary infection which is confined to the surface of the skin can be easily documented with a bacterial culture. Systemic infection is proven by one or more blood cultures and is usually accompanied by the presence of an abnormal white blood cell count.

Managing Blisters – Because blisters in EB are not self limiting, and can fill with fluid and grow quite large, they need to be drained . They may also be associated with considerable pain and result in limitations for the patient. Blisters on the soles of the feet, for example, may prevent an affected individual from walking or even standing.

The preferred approach is to first gently cleanse the blister's surface with isopropyl alcohol, followed by its lancing with a small sterile needle. If the latter cannot be obtained or afforded, then a reasonable alternative is to use a fine, clean, sewing needle which has been kept immersed in isopropyl alcohol and then dried and briefly sterilized by careful heating over a lit match or flame until its tip is yellow. It can then be used as soon as it is again cool. Once the punctured blister has been drained of its contents by the gentle application of pressure with a clean gauze pad, a tiny dab of a mild antibiotic ointment should be placed over the puncture site, followed by application of a sterile dressing, so as to reduce the risk of secondary infection. If necessary, a blister can be drained numerous times, if it repeatedly re-fills with fluid. Oral blisters will often open during meals.

Managing Pain and Itching-- Patients with EB frequently experience painful blisters and open sores. When necessary brief courses of appropriate analgesics may be prescribed, although the chronic use of codeine-containing medications as well as other narcotics may cause or worsen pre-existing constipation, which is also a

common complication of the more severe forms of inherited EB. Itching may be a sign of secondary infection, although it can also occur in its absence. Systemic antihistamines may be helpful to address itching.

Gastrointestinal and Nutritional Issues - Dysphasia and constipation are common problems for EB patients. They may be caused by erratic eating patterns, low fluid and fiber intake, as well as extensive blistering leading to increased fluid requirements. Soft tissue injury in the mouth, trouble chewing, swallowing, problems with dentition, esophageal scarring and/or webbing all contribute to poor dietary intake of fiber containing foods such as cereals, breads, fruits and vegetables. In addition, most iron supplements have been known to contribute to constipation. And, since the gastrocolonic reflex is stimulated by ingestion of food, avoidance of eating, apathy and loss of appetite worsen the nutritional status. Input by a pediatric dietitian/nutritionist can be helpful in formulating a dietary regimen that reduces constipation and/or fecal impaction.

Good nutrition is an important part of wound healing but often difficult to achieve in people with EB. Additional calories and nutrition should be added to meals whenever possible through use of protein and fiber powders. Foods should also be available in consistencies that are easy to chew, swallow and digest.

Esophageal strictures can occur frequently in more severe forms of EB and can cause tremendous problems in the health and well-being of the person with EB. Balloon esophageal dilations are commonly done in this population. In evaluating an EB patient for stricture, it is important to include the request for an evaluation of the entire esophagus from the oropharynx through the gastroesophageal junction as significant strictures occur in the proximal cervical esophagus and can be overlooked in a less thorough exam.

Clothing – In younger children, diapers may require additional padding at the legs and waist. Clothing such as garments with tight elastic bands and non-padded shoes, should be avoided, since blisters may readily form in these particular areas. Whenever possible, loose-fitting garments should be worn. If blisters develop as a result of friction from the seams of clothing, garments may be worn inside-out and tags, cuffs and necklines may be removed. Tight-fitting shoes, especially those with leather soles, frequently result in the induction of blisters in patients with EB. More loose fitted, padded shoes, preferably those with rubber soles, are generally better tolerated.

Monitoring for Cancer - Squamous Cell Carcinoma is the leading cause of death in EB outside of infancy. Patients with Recessive dystrophic EB (RDEB), are at increased risk of developing skin cancers during their lifetimes. Maintain a **High Index of Suspicion** with any chronically non-healing skin sores. Primary SSC occurs in multiple sites in this population and 80% of RDEB patients die within 5 years of diagnosis.

It is very important that all EB patients have at least yearly examination of all skin areas. Furthermore, any skin sore which is not healing like other lesions should be immediately brought to the attention of the patient's dermatologist and biopsied to exclude the presence of early malignancy.

Anemia and Mineral deficiencies : Many children with EB become anemic due to a chronic loss of blood through wounds, poor nutritional intake and poor absorption. Treatment for iron deficiency anemia is often necessary. Many children continue supplemental iron even after the anemia has been corrected to prevent recurrence. Many commercial nutritional supplements contain iron.

Recently, connection has been seen in selenium and carnitine deficiencies and cardiomyopathy, and some EB physicians now prescribe supplements for these as well.

Testing Resources: It is important to call the lab that will be utilized prior to specimen collection.

Beutner Labs, Inc. 3436 Avenue, P.O. Box 26 Buffalo NY, 14215-0026 (716) 838-0549
E-mail: www.beutnerlabs.com

Stanford Dermatopathology Service
Department of Pathology - H2110
Stanford Medical Center
300 Pasteur Drive Stanford, CA 94305 650-723-6736
E-mail: dermatopathology@lists.stanford.edu


GeneDx 207 Perry Parkway Gaithersburg, MD 20877 301-519-2100 (www.genedx.com)

How Does DebRA Help?



DebRA was organized thirty years ago as a national, nonprofit organization. The mission of DebRA is to find a cure for Epidermolysis Bullosa and to improve the health and well being of all individuals and families in the world affected by all forms of the disorder.

Its program of services includes a Nurse Educator, a National Medical Provider referral service, free emergency supplies and financial assistance, a network of regional support groups and an informational website. DebRA promotes and supports an extensive international scientific research effort. Resources in Spanish are also available.

You may contact DebRA of America with questions:

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To Reach the DebRA Nurse Educator:

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